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Effect of sex on anticoagulant use for stroke prevention in atrial fibrillation: registry with 4,099 patients from a tertiary cardiology centre

Wpływ płci na zalecanie doustnej antykoagulacji w prewencji powikłań zakrzepowo-zatorowych u chorych z migotaniem przedsionków — rejestr 4099 chorych z referencyjnego ośrodka kardiologicznego*

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Abstract

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. AF is characterised by disorganised atrial activation which leads to an impairment of atrial haemodynamic function and, in turn, to serious clinical consequences such as increased risks of heart failure, thromboembolism, and death. AF prevalence increases with age; in people aged < 50 years, the prevalence is 0.1%, whereas in those aged > 85 years it is 17.8%. Although men have a higher risk of AF compared to women, in women, AF more often is symptomatic and associated with more serious complications. Because female sex is a risk factor for thromboembolism, in 2012 the European Society of Cardiology recommended the use of the CHA_2DS_2-VASc score, which scores 1 point for being female, in assessing the thromboembolic risk in patients with AF.

Among hospitalised patients with AF (men and women), this study assessed the thromboembolic risk and evaluated anticoagulant use for stroke prevention.

Key words: stroke, atrial fibrillation, sex

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Praca powstała w ramach realizacji projektu: „Zakup wyposażenia I Klinicznego Oddziału Kardiologii i Pracowni Elektrofizjologii szansą na zwiększenie innowacyjności Wojewódzkiego Szpitala Zespolonego w Kielcach" współfinansowanego przez Unię Europejską ze środków Europejskiego Funduszu Rozwoju Regionalnego w ramach Regionalnego Programu Operacyjnego Województwa Świętokrzyskiego na lata 2007–2013

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Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. AF is characterised by disorganised atrial activation which leads to an impairment of atrial haemodynamic function and, in turn, to serious clinical consequences such as increased risks of heart failure, thromboembolism, and death [1–3]. AF prevalence increases with age; in people aged < 50 years, the prevalence is 0.1%, whereas in those aged > 85 years it is 17.8% [4]. Although men have a higher risk of AF compared to women, in women, AF more often is symptomatic and associated with more serious complications. Because female sex is a risk factor for thromboembolism, in 2012 the European Society of Cardiology recommended the use of the CHA_2DS_2-VASc score, which scores 1 point for being female, in assessing the thromboembolic risk in patients with AF [5].

Among hospitalised patients with AF (men and women), this study assessed the thromboembolic risk and evaluated anticoagulant use for stroke prevention.

Material and methods

Study population and inclusion criteria

This retrospective study analysed data of patients with AF who were hospitalised between 2004 and 2012 in a tertiary cardiology centre. The hospitalisations were due to elective procedures or emergency admissions.

The inclusion criterion was AF diagnosed during hospitalisation.

The exclusion criteria were: valvular AF, in-hospital death, and incomplete data. In cases of multiple hospitalisations, data from the most recent hospitalisation was analysed.

Because the analysed data was acquired in 2004–2012, the $CHADS_2$ scores were used for thromboembolic risk assessment. The $CHADS_2$ scores assessed the following factors: stroke, transient ischaemic episode or peripheral embolism, age ≥ 75 years, hypertension, diabetes, and heart failure. The CHA_2DS_2-VASc scores were calculated retrospectively. In addition to the $CHADS_2$ score, the CHA_2DS_2-VASc scores assessed the following factors: female sex, age 65–74 years, and vascular diseases.

Other variables

The HAS-BLED scale was used for bleeding risk assessment in patients with AF. The scale assessed the following factors: hypertension, abnormal liver or kidney function, prior stroke, prior bleeding or factors predisposing to bleeding, labile international normalised ratio (INR), age ≥ 65 years, use of antiplatelet drug(s) or non-steroidal anti-inflammatory drugs, and alcohol abuse.

The glomerular filtration rate, calculated based on the Modification of Diet in Renal Disease Study formula, indicated kidney function.

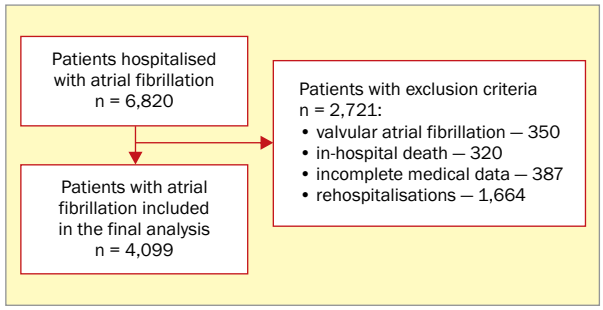

Figure 1. Flow chart of patient enrolment in the current analysis

Statistical methods

Univariate and multivariate logistic regressions assessed prognostic properties of the analysed variables.

Statistical significance was interpreted as follows:

- for $p < 0.001$, high statistical significance;
- for p 0.001–0.005, statistical significance;
- for p 0.05–0.1, statistical trend,

Med. Calc Ver. 12.4.0.0. software was used for all calculations.

Results

Among 6,820 patients discharged with AF in 2004–2012, 4,099 patients with non-valvular AF were enrolled (Figure 1), including 1,855 (42.3%) women and 2,244 (54.7%) men ($p < 0.0001$). The mean age was 70.6 years (± 10.9); in men the mean age was 68.2 (± 11.5); in women it was 73.5 (± 9.4). There were 1,701 (41.5%) patients aged > 74 years (Table 1).

Paroxysmal AF was the most frequent AF type (1,875 patients, 45.7%; 925 women, 49.9%; 950 men, 42.4%, $p < 0.0001$). Permanent AF was found in 1,767 patients (43.1%); 765 (41.2%) women, 1,002 men (44.6%); $p = 0.0337$. Thirty patients (0.7%) had newly diagnosed AF (19 women, 1.0%; 11 men, 0.5%; $p = 0.0606$). Persistent AF was found in 427 patients (10.4%); 146 women, 7.9%; 281 men, 12.5%; $p < 0.0001$. Table 1 presents the frequency of comorbidities in the studied patients.

Women had a higher thromboembolic risk than men did. A high thromboembolic risk was found in 1,374 women (74.1%) and 1,385 men (61.7%) based on the $CHADS_2$ score, and in 1,809 (97.5%) women and 1,799 (80.2%) men based on the CHA_2DS_2-VASc score (Table 2).

For thromboembolic prophylaxis, at discharge, 2,626 (64%) patients (1,167 women, 62.9%; 1,429 men, 63.6%) received an oral anticoagulant (OAC) alone or in combination with antiplatelet drugs; 821 (20%) patients (383 women, 20.6%; 438 men, 19.5%) received acetylsalicylic acid (ASA) alone; 87 (2.1%) patients (38 women, 1.6%; 49 men, 2.2%) received low-molecular-weight heparins; 42 (1%) patients (21 women, 1.1%; 21 men, 0.9%) received clopidogrel alone; and 243 (59%) patients (126 women, 6.8%; 117 men, 5.2%) received no antiplatelet drugs or anticoagulants (Table 3).

Table 1. Clinical characteristics of hospitalised women and men with atrial fibrillation

Clinical characteristic	Total N = 4,099	Women N = 1,855	Men N = 2,244	p
Age:				
• mean (SD), years	70.6 (± 10.9)	73.5 (± 9.4)	68.2 (± 11.5)	< 0.0001
Age group:				
• ≤ 50 years	3.4%; 139/4,099	1.1%; 20/1,855	5.4%; 119/2,244	< 0.0001
• 50–64 years	24%; 985/4,099	16.2%; 300/1,855	30.5%; 685/2,244	< 0.0001
• 65–74 years	31.1%; 1,274/4,099	30.1%; 571/1,855	31.3%; 703/2,244	NS
• ≥ 75 years	41.5%; 1,701/4,099	52%; 964/1,855	32.8%; 737/2,244	< 0.0001
Medical history:				
• hypertension	74.8%; 3,067/4,099	81.4%; 1,511/1,855	69.3%; 1,556/2,244	0.0001
Coronary artery disease:	56.7%; 2,324/4,099	55.1%; 1,023/1,855	58%; 1,301/2,244	NS
• previous myocardial infarction	27.2%; 1,116/4,099	22.7%; 421/1,855	31%; 695/2,244	< 0.0001
• acute coronary syndrome	8.5%; 349/4,099	8.2%; 152/1,855	8.8%; 197/2,244	NS
• previous percutaneous coronary intervention	9.5%; 390/4,099	7.8%; 144/1,855	11%; 246/2,244	0.0005
Previous coronary artery by--pass grafting	3.7%; 152/4,099	1.9%; 36/1,855	5.2%; 116/2,244	< 0.0001
Heart failure	54.8%; 2,247/4,099	53.4%; 991/1,855	56%; 1,256/2,244	NS
Impaired renal function (GFR < 60 ml/min)	53.8%; 2,206/4,099	68.6%; 1,273/1,855	41.6%; 933/2,244	< 0.0001
Dyslipidaemia	19.8%; 811/4,099	20.8%; 386/1,855	18.9%; 425/2,244	NS
Diabetes mellitus type 2	21.8%; 893/4,099	24.2%; 448/1,855	19.8%; 445/2,244	0.0007
Thyroid disease	7.4%; 304/4,099	8.4%; 156/1,855	6.6%; 148/2,244	0.0286
Chronic obstructive pulmonary disease	4.2%; 173/4,099	3.7%; 68/1,855	4.7%; 105/2,244	NS
Malignancy	1.9%; 79/4099	0.6%; 12/1855	3.0%; 67/2244	< 0.0001
Previous thromboembolism:				
• stroke	10.6%; 434/4,099	11.9%; 220/1,855	9.5%; 214/2,244	0.0129
• transient ischaemic attack	1.4%; 59/4,099	1.6%; 29/1,855	1.3%; 30/2,244	NS
• other thromboembolism	2%; 80/4,099	2.4%; 44/1,855	1.6%; 36/2,244	NS

SD — standard deviation; NS — not significant; GFR — glomerular filtration rate

Among 2,626 patients who received an OAC alone or in combination with antiplatelet drugs, 180 (60.6%) had $CHADS_2$ = 0.658 (63.2%) had $CHADS_2$ = 1, and 1,788 (64.8%) patients had $CHADS_2 \geq 2$ points. Among 1,142 patients who received antiplatelet drug(s), 82 (27.6%) had $CHADS_2$ = 0 points, 297 (28.5%) patients had $CHADS_2$ = = 1 point, and 764 (27.7%) patients had $CHADS_2 \geq 2$ points. Among 248 patients discharged without any stroke prophylaxis, 28 (9.4%) patients had $CHADS_2$ = 0 points, 70 (6.7%) patients had $CHADS_2$ = 1 point, and 145 (5.7%) patients had $CHADS_2 \geq 2$ points. Figure 2 presents stroke prophylaxis choices in women and men.

Discussion

In this study, 55% of hospitalised patients with AF were male. Compared to women, the proportion of men was also higher in the ATRIUM registry [6], the Euro Heart Survey on Atrial Fibrillation [7], and the Registry of the German Competence NETwork on Atrial Fibrillation [8]. In another study, of 613 patients discharged from a regional hospital, 51% were female [9]. In that study, the mean patient age was 74.3 years, compared to 70.6 in our study; thus, the difference in sex distribution between our study and that study could be explained by the fact that AF prevalence in old age is

Table 2. Thromboembolic and bleeding risk of hospitalised women and men with atrial fibrillation

Variable	Total N = 4,099	Women N = 1,855	Men N = 2,244	p
$CHADS_2$				
Mean ± SD	2.2 ± 0.7	2.4 ± 4.24	2.02 ± 2.12	< 0.0001
Median	2.5	3	1	< 0.0001
0 points	7.2%; 297/4,099	4.9%; 90/1,855	9.2%; 207/2,244	< 0.0001
1 point	25.4%; 1,042/4,099	21%; 390/1,855	29.1%; 652/2,244	< 0.0001
≥ 2 points	67.4%; 2,760/4,099	74.1%; 1,375/1,855	61.7%; 1,385/2,244	< 0.0001
CHA_2DS_2-VASc				
Mean ± SD	3.7 ± 0.7	4.5 ± 4.95	2.98 ± 1.41	< 0.0001
Median	3.5	4.5	3.5	< 0.0001
0 points	3.1%; 127/4,099	–	56.6%; 127/2,244	–
1 point	8.9%; 364/4,099	2.5%; 46/1855	14.2%; 318/2,244	< 0.0001
≥ 2 points	88%; 3,608/4,099	97.5%; 1,809/1,855	80.2%; 1,799/2,244	< 0.0001
HAS-BLED				
Mean ± SD	2.1 ± 0.7	2.4 ± 2.12	1.9 ± 1.02	< 0.0001
Median	3	0	2	< 0.0001
0–2 points	65.4%; 2,681/4,099	55.1%; 1,023/1,855	73.9%; 1,658/2,244	< 0.0001
≥ 3 points	34%; 1,418/4,099	44.9%; 832/1855	26.1%; 586/2,244	< 0.0001

CHA_2DS_2-VASc — cardiac failure or dysfunction, hypertension, age ≥ 75 [double], diabetes mellitus, stroke [double]-vascular disease, age 65–74, and sex category [female]; SD — standard deviation; $CHADS_2$ — congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and previous stroke or transient ischaemic attack [double]; HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history, or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly

Table 3. Comparison of differences in antithrombotic prophylaxis between men and women

Treatment	Total N = 4,099	Women N = 1,855	Men N = 2,244	p
Anticogulant treatment (OAC)				
VKA (monotherapy)	57%; 2,336/4,099	58.3%; 1,081/1,855	55.9%; 1,255/2,244	NS
VKA + ASA + clopidogrel	3%; 125/4,099	2.7%; 50/1,855	3.3%; 75/2,244	NS
VKA + ASA	2.8%; 116/4,099	1.6%; 30/1,855	3.8%; 86/2,244	< 0.0001
VKA + clopidogrel	0.4%; 18/4,099	0.3%; 5/1,855	0.7%; 13/2,244	NS
Dabigatran	0.4%; 18/4,099	0.5%; 10/1,855	0.4%; 8/2,244	NS
Rivaroxaban	0.3%; 14/4,099	0.1%; 2/1,855	0.5%; 12/2,244	0.0238
Antiplatelet treatment				
ASA (monotherapy)	20%; 821/4,099	20.6%; 383/1,855	19.5%; 438/2,244	NS
Clopidogrel (monotherapy)	1%; 42/4,099	1.1%; 21/1,855	0.9%; 21/2,244	NS
ASA + clopidogrel	6.8%; 279/4,099	5.9%; 109/1,855	7.6%; 170/2,244	0.0318
Other				
Low molecular weight heparin	2.1%; 87/4,099	1.6%; 38/1,855	2.2%; 49/2,244	NS
Without prophylaxis	5.9%; 243/4,099	6.8%; 126/1,855	5.2%; 117/2,244	0.0308

OAC — oral anticoagulant; VKA — vitamin K antagonist; NS — not significant; ASA — acetylsalicylic acid

higher in women than in men, possibly because women have a longer life expectancy than men. In two studies performed in Turkey among patients with AF, women also outnumbered men (RMASES study, 55.9%; AFTER study, 60% [10, 11].

In this study, hypertension was the most common thromboembolic risk factor, and it affected women significantly more often than men (75% vs 69%). Thus, our results are in line with the GARFIELD study, in which women, too, had

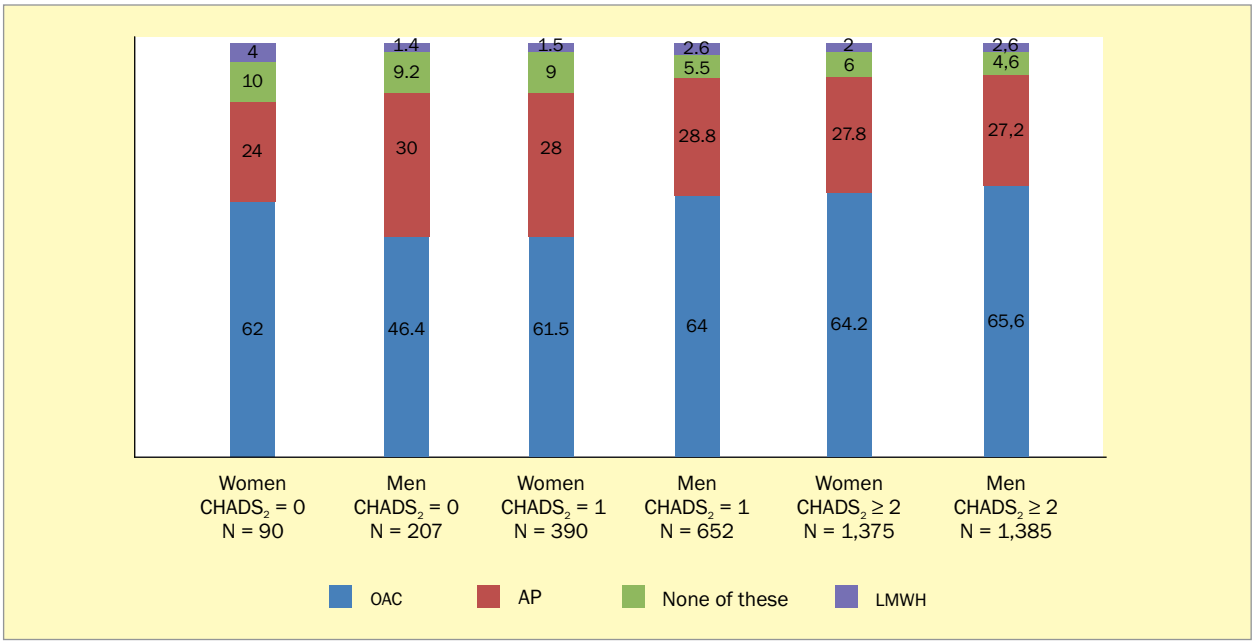

Figure 2. Antithrombotic prophylaxis in men and women according to score on $CHADS_2$ (congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and previous stroke or transient ischaemic attack [double]) scale; OAC — oral anticoagulant; AP — antiplatelets; LMWH — low-molecular-weight heparin

hypertension more often than men (24% vs 20%) [12]. Also, compared to men, women more often had impaired kidney function (69% vs 42%) and type 2 diabetes (24% vs 20%). In this study, a significant proportion of patients with AF, both men and women, had ischaemic heart disease. Patients with AF in the Bialystok registry had a similar prevalence of ischaemic heart disease [13]. In this study, men more often than women had prior myocardial infarction, percutaneous coronary interventions, or coronary artery bypass grafting, which is in line with previous studies (GARFIELD [12], Euro Heart Survey on AF [7], GulfSAFE [14]). Female sex is an established cardiovascular risk factor. In this study, women more often than men had prior ischaemic stroke, but prior transient ischaemic attacks or peripheral embolism were equally common in men and women. A study from the GulfSAFE registry found that women more often than men had prior ischaemic attacks, but the rate of prior stroke did not differ between the sexes [16]. In the PREFER in AF registry, women, compared to men, had more thromboembolic complications [15]. Excluding women with lone AF aged < 65 years, female sex is an independent thromboembolic risk factor [16, 17]. Thus, in 2012 the European Society of Cardiology recommended the use of the CHA_2DS_2-VASc score, which scores 1 point for being female, for thromboembolic risk assessment in patients with AF [5].

Because this study analysed data of patients hospitalised in 2004–2012, the $CHADS_2$ score was used for thromboembolic risk assessment; however, the CHA_2DS_2-VASc scores were calculated retrospectively. A high thromboembolic risk was found in 74% of women and 62% of men based on the $CHADS_2$ score, and in 98% of women and 80% of men based on the CHA_2DS_2-VASc score. Because in the CHA_2DS_2-VASc score one point is given for being female, women had higher scores than men did. However, cardiovascular diseases, which, in our study, were more common in men than in women, are also included as a risk factor in the CHA_2DS_2VASc score. High $CHADS_2$ and CHA_2DS_2-VASc scores were also more common in women than in men due to a higher frequency of age ≥ 75 years, hypertension, diabetes, and prior stroke among women. A high thromboembolic risk was also more common in women than in men in earlier studies (Euro Heart Survey on AF [7], GARFIELD-AF [12, 18], Gulf SAFE [14], PREFER in AF [15]).

In our study, OACs alone were prescribed to men and women equally often, which is in line with studies from the GARFIELD-AF and Euro Heart Survey on AF registries that were performed in a similar period as this study [7, 12]. In the PREFER IN AF registry featuring 7,243 patients enrolled in 2012–2013, 95% of men and women received OACs [15]. In our study, men and women received ASA alone, or clopidogrel alone, at a similar frequency, but men were more likely to receive dual antiplatelet therapy due to a higher incidence of ischaemic heart disease. Interestingly, a higher proportion of women than men received no stroke prophylaxis (6.8% vs 5.2%). Among Swedish patients with AF, in 2007–2011, 17% received no stroke prophylaxis, both men and women, and in 2011–2015 that figure was 15% in women and 17% in men [19]. Because the thromboembolic risk in this study was higher in women than in men, one could expect that women would be more likely to

receive anticoagulants; however, because the bleeding risk was also higher in women than in men, women were more likely than men to receive no anticoagulation.

Conclusions

1. Among hospitalised patients with AF, women were older than men. 2. High thromboembolic risk was found more frequently in women than in men, according to both the CHA_2DS_2-VASc and $CHADS_2$ scores. 3. Among patients with AF, women were more likely than men to receive no stroke prophylaxis at discharge, whereas men were more likely than women to receive double antiplatelet therapy or an antiplatelet drug in combination with a vitamin K antagonist, possibly due to a higher incidence of ischaemic heart disease in men.

Streszczenie

Migotanie przedsionków (AF) jest najczęściej występującą arytmią, zarówno u mężczyzn, jak i u kobiet, polegającą na nieskoordynowanym pobudzeniu przedsionków, któremu może towarzyszyć szybka akcja komór. W Stanach Zjednoczonych dotyka 1% dorosłych. Częstość występowania AF wzrasta istotnie z wiekiem i w populacji chorych powyżej 80. roku życia sięga aż 9%. Częściej na AF chorują mężczyźni, natomiast u kobiet arytmia ta częściej przebiega objawowo i jest obarczona groźniejszymi powikłaniami. Czynniki ryzyka AF z podobną częstością występowały u kobiet i mężczyzn, jednak w ostatnich badaniach wykazano częstsze występowanie nadciśnienia tętniczego w grupie kobiet. U kobiet częściej występują powikłania zakrzepowo-zatorowe, dlatego płeć żeńska jest elementem ocenianym w skali CHA_2DS_2-VASc jako czynnik ryzyka zakrzepowo-zatorowego.

Celem pracy jest ocena czynników ryzyka zakrzepowo-zatorowego u hospitalizowanych kobiet i mężczyzn z AF.

Słowa kluczowe: udar mózgu, migotanie przedsionków, płeć

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